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ORIGINAL PAPER

Assessment of vascular leakage and its development with FFA among patients treated with intravitreal anti-VEGF due to aggressive posterior ROP

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Abstract

Objective Evaluation of vascular leakage and retinal vascular development with fundus fluorescein angiography for infants diagnosed with aggressive posterior retinopathy of prematurity who underwent intravitreal anti-VEGF treatment.

Method Medical recordings of 30 patients who received RetCam fluorescein angiography during follow-up and had been treated with anti-VEGF on diagnosis of aggressive posterior ROP in the zone I or zone II between the dates of April 2014–January 2017 were evaluated retrospectively.

Results Fifty-nine eyes of 30 patients were included in the study. Mean birth weight was 1145 g; gestation week was 28.4. Recurrence occurred in 30.5% of the patients, and 10.1% of them were given a second dose of injection of anti-VEGF. Leakage was detected in 15.3% of the eyes during angiography, and all of these eyes were treated with laser photocoagulation. Evaluation of vascular development revealed that in the temporal, complete retinal vascular development was achieved in only 8% of the eyes. It was detected that complete retinal vascularization was not observed in any of the cases which were given second dose of injection due to recurrence. The patients were distributed into groups according to postmenstrual week taken to angiography as 32 eyes of 16 patients in group 1, 17 eyes of 9 patients in group 2 and 10 eyes of 5 patients in group 3. The vascular leakage rate of group 3 patients was statistically significantly higher ($p < 0.05$) and vascular development between groups was not statistically significant ($p > 0.05$).

Discussion With the initiation of FFA usage in pediatric cases, especially treated with anti-VEGF due to retinopathy of prematurity (ROP), more findings (vascular arrest, leakage, and abnormalities, etc.) are obtained than those achieved via ophthalmoscopic examination. In the light of these findings, early intervention with laser photocoagulation in early stages becomes possible enabling prevention of possible blindness.

Keywords Intravitreal anti-VEGF · Aggressive posterior ROP · Vascular leakage · Fundus fluorescein angiography

Introduction

Retinopathy of prematurity (ROP) is a vascular disease of the retina that affects premature neonates and may possibly result in blindness. It takes the first place among the leading causes of preventable childhood blindness [1]. Treatment is required in approximately 10% of infants developing ROP, but blindness

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develops nevertheless in some of these infants despite the treatment [2]. The gold standard of ROP treatment is the ablation of peripheral avascular retina [3, 4]. When it was proven that VEGF-A had a key role in the pathogenesis of the disease, the usage of bevacizumab started as anti-VEGF agent in ROP treatment (Avastin; Genentech, South San Francisco, CA) in monotherapy, rescue treatment, or combined treatment with laser [4–11]. Especially in the treatment of the severely progressing form of aggressive posterior ROP (APROP), implementation of laser photocoagulation may be hindered due to pupillary rigidity, vitreous haze, presence of persistent pupillary membrane, or indistinct demarcation line between vascular and avascular retina. Furthermore, due to high repetitive laser pulse requirement and the destruction of a wide retinal area, anti-VEGF (vascular endothelial growth factor) treatment is preferred by many physicians rather than the laser photocoagulation application [12, 13]. The disease shows rapid regression with treatment that has an increasing frequency of usage today, but long-term local and systemic side effects related to the treatment are not clearly known. In addition, the inability to determine exactly how and how often the follow-up will be performed with the patients, the reports of late term recurrences, and especially this treatment being off-label in premature infants constitute the restrictive aspects of this treatment.

In recent years, imaging systems that allow capturing images of fundus fluorescein angiography (FFA) in infants provide understanding of the pathogenesis of ROP and especially vascular changes in macular and peripheral retina in infants that were given anti-VEGF treatment [14–16]. Thanks to this diagnostic method, it has been easier to follow-up the retinal vascularization of the infants who were given the intravitreal injection, to detect retinal vascular abnormalities, and to specifically spot the recurrences, which cannot be identified by ophthalmoscopy. Currently, the FFA has almost become the gold standard in the follow-up of ROP cases treated with intravitreal anti-VEGF. In this article, as we share the FFA findings of APROP infants treated with intravitreal anti-VEGF, we hope to contribute additional evidences on this field.

Method

The study was performed with the retrospective examination of the files of infants who underwent intravitreal bevacizumab (IVB) treatment on the diagnosis of aggressive posterior ROP between April 2014 and January 2017 and whose FFA were taken during the follow-ups. Fifty-nine eyes of 30 patients who were followed up for at least 30 weeks post-injection were included in the study. One eye that had an early recurrence after anti-VEGF treatment and underwent laser photocoagulation was excluded from the study. The diagnosis of aggressive posterior ROP was made with the joint decision of at least two experienced ophthalmologists, as defined in the International Classification of ROP (zone I–II posterior localization, plus disease presence in four quadrants, accompanied by flat neovascularization in some cases, the type of ROP with the absence of the classical phases) [17]. For the 30 patients treated with IVB, weeks of gestational age, birth weight, the disease zone, the week of treatment, and the postmenstrual week at the time when the FFA was taken were recorded. Patients were divided into three groups according to PMW taken to FFA (group 1 was under 96th PMW, group 2 was between 96 and 126 PMW, group 3 was over 126th PMW) in order to compare vascular development and leakage.

Injection technique

The patients were treated within 24 h after being diagnosed with APROP at ROP Diagnosis and Treatment Center of Istanbul Kanuni Sultan Süleyman Education and Research Hospital. IVB injection was performed in the operating room under local anesthesia, monitorized by an experienced anesthesiologist. The eye was stained with betadine after which sterile lid speculum was inserted and washed with 5% povidone iodine. 0.650 mg/0.025 ml (50% of adult dose) of bevacizumab was administered at a distance of 1.5 mm from the limbus with a 30 gauge 4-mm microneedle. Topical moxifloxacin (Vigamox) drops were used once per hour throughout the first day post-injection, and 6 times a day during the following days for 1 week. After injection, the patients were examined on the 1st day, then on the 1st week, and then weekly until the disease was completely regressed. The follow-ups were based on the status of

vascularization of the infant and according to the relapse status of the disease.

FFA technique

FFA was performed on the patients with RetCam III (Clarity Medical Systems, Pleasanton, CA) device at Istanbul Bakirkoy Sadi Konuk Education and Research Hospital ROP Diagnosis and Treatment Center. After general anesthesia was performed by an experienced anesthesiologist, bilateral wide-angle fundus pictures and fluorescein angiographies were taken with the device from all infants. After application of intravenous bolus 0.05 ml/kg 10% sodium fluorescein (Alcon Pharma GmbH, 79108 Freiburg, Germany), FFA was performed via introduction as 3.0 ml isotonic saline push. According to FFA images, the region of ending of vascularization and the presence of vascular leakage were noted.

Lorenz et al. identified certain coefficients to prove the completion of retinal vascular development according to the morphological criteria detected on the FFA made to a 30 weeks old infant born at term. Accordingly, with the distance between optic nerve central and fovea taken as a unit, vascularization of four units in the nasal and five units in the temporal indicated the completion of vascular development [18]. However, within their own study they also considered the presence of retinal vascularization of three units in the nasal, four units in the temporal as complete retinal vascular development. In our study, retinal vascularization measurements of the patients were taken according to these calculations.

Statistical analysis

For statistical analysis SPSS (SPSS Inc., PASW Statistics for Windows, Version, 18.0, Chicago, USA) program was used. The conformity of data to normal distribution was evaluated by using Kolmogorov–Smirnov and Shapiro–Wilk tests. The parameters which did not comply with normal distribution were compared with Mann–Whitney *U* test. Comparison between groups was evaluated by Kruskal–Wallis test.

Results

In the study, 59 eyes of 30 patients treated with intravitreal bevacizumab on diagnosis of APROP and followed-up for at least 30 weeks post-treatment were included. 50% of the patients ($n = 15$) were female; 50% of them ($n = 15$) were male. The patients were at the mean gestational week range of 28.4 ± 2.6 (24–33); mean birth weight was 1145 ± 371.6 g (360–1800 g). In 14 of the 59 eyes diagnosed with APROP (23.7%), vascularization was at zone II, and in 45 of them (76%) it was at zone I. IVB was applied to the patients at the mean postmenstrual week of 34.9th (32–40 weeks) (PMW). No local or systemic complications were observed in the patients related with the injection.

In 19 of the 60 eyes (31.6%) recurrence occurred during follow-ups. Recurrence was detected at the mean postmenstrual week of 44.2th PMW (40–49 PMW). One of the 60 eyes underwent laser photocoagulation application after early recurrence, and this eye was excluded from the study. Among the 59 eyes included in the study, recurrence occurred in 18 (30.5%) of them, and 6 (10.1%) of these were given a second dose of anti-VEGF treatment after recurrence as type 1 ROP. Mean birth weight of the infants receiving the second dose of IVB was 773 ± 466 g (360–1360), and they were at the mean gestational age of 27.3 ± 2.2 (25–30) weeks. Although the birth weight and gestational week of infants receiving the second dose of IVB were lower in comparison with those of the infants who had single dose, this difference was not found to be statistically significant ($p > 0.05$). Second dose of IVB for recurrence was applied at the mean PMW of 47th week (46–49). The other 12 recurrences (20.3%) were followed up without any further treatment, and spontaneous remission was observed in these cases (Fig. 1).

The FFA was applied to the patients with the RetCam III (Clarity Medical Systems, Pleasanton, CA) that was newly introduced for usage in our clinic, at their mean postmenstrual week of 102.4th (66–167) PMW. Therefore, PMW of patients evaluated with FFA vary. Only one patient (3.3%) developed bronchospasm related to the procedure. No additional complications were observed. Occurrence of vascular leakage and status of retinal vascularization according to the study of Lorenz et al. [18] were evaluated with the FFA. Vascular leakage was detected in 9 (15.3%)

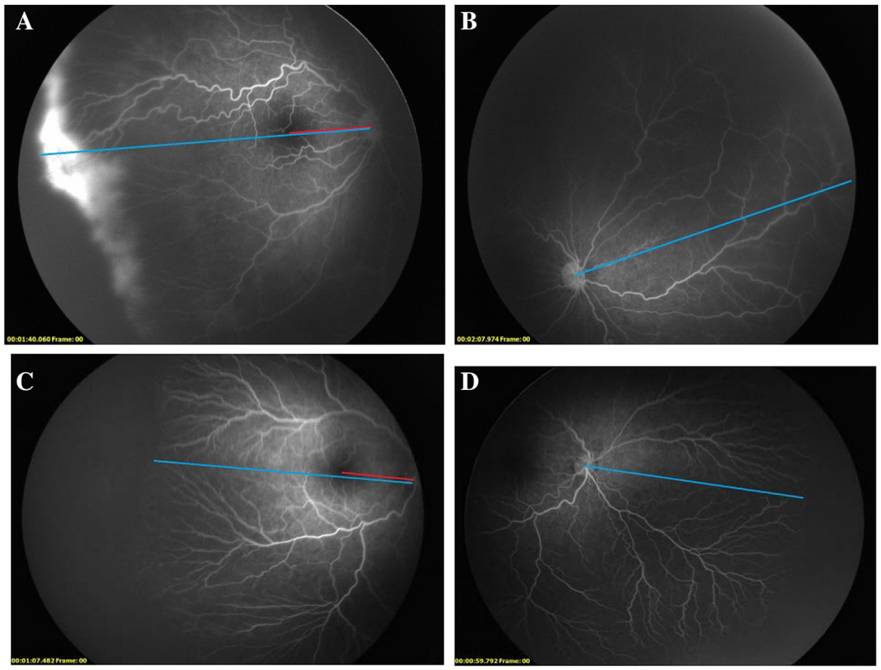

Fig. 1 **a** Fluorescein angiography image of the patient 7. The red line shows the distance from the center of the disk to the fovea and the blue line shows the distance from the center of the optic disk to the border of the vascularized zone. The leakage of fluorescein was seen from neovascularization at the vascular–avascular junction. **b** Nasal border of retinal vascularization of the same patient. **c** FFA image of the patient number 27. Right eye's temporal border of vascularization and large avascular periphery were seen. **d** Nasal border of retinal vascularization and avascular periphery of the same patient

of the 59 eyes, and all of these eyes underwent laser photocoagulation application. No treatment was applied to the remaining 50 eyes, and it was planned to apply FFA to the patients in order to monitor the vascular development of the patients every 6 months, and to apply laser photocoagulation to the infants whose vascularization would fall short of reaching the confidence interval.

In regard with the study of Lorenz et al. mean rate of nasal retinal vascularization was determined as 3.68 ± 0.33 units and that of temporal retinal vascularization as 4.16 ± 0.44 units (18). Four units of nasal retinal vascularization were detected in 23 eyes (38%), and 5 units of temporal vascularization were detected in 5 eyes (8%). Again in view of the same study specifying the extent of acceptable retinal vascularization (of 3 units in the nasal, of 4 units in the temporal), it was observed that vascularization of 3 units or above was present in the nasal in all of the eyes. However, vascularization of 4 units or above in the temporal was detected on 39 eyes (66%). In 20 eyes (34%), vascularization was observed to be below 4 units (Table 1).

Regarding the 6 eyes which developed recurrence during follow-ups and were treated with a second dose of anti-VEGF, the nasal rate was found to be 3.5 ± 0.18 units (3.3–3.8), and the temporal rate was found to be 3.7 ± 0.2 units (3.45–4.18). These results indicate that no eyes develop complete retinal vascularization in the nasal or temporal. But in view of the acceptable criteria of retinal vascularization, it was observed that all eyes (100%) developed acceptable vascularization in the nasal, while in the temporal only one eye (16.7%) did so. When infants receiving single dose and two doses of IVB were taken as separate groups and compared to each other, the temporal vascularization of the group with the second IVB application was observed to be left further behind than that of the single dose group ($p < 0.004$).

The patients were distributed into groups according to PMW as 32 eyes of 16 patients in group 1, 17 eyes of 9 patients in group 2 and 10 eyes of 5 patients in group 3. The mean gestational age was 28.4 ± 2.6 (24–33) in group 1, 28.8 ± 3.1 (24–32) in group 2, and 29.0 ± 1.76 (27–31) in group 3. Birth weights were 1153.6 ± 392.6 g (360–1800), 1092.3 ± 428.6 g (500–1750), 1206 ± 144.1 g (1030–1400), respectively. There was no statistically significant difference between groups when we compared gestational age with birth weight ($p > 0.05$).

Vascular leakage was observed in 2 eyes (6.1%) in group 1, in 3 eyes (18.8%) in group 2 and in 4 eyes (40%) in group 3. Although the distribution between the groups was uneven and the number of patients was

Table 1 Results of the relative distances to the temporal and nasal border of vascularization at the time of the last follow-up with FA in 30 patients with retinopathy of prematurity after monotherapy with 0.625 mg intravitreal bevacizumab

Patient no.	Weeks after IVB	OD temp ratio	OD nasal ratio	OS temp ratio	OS nasal ratio
1	90	4.30	3.6	3.8	3.3
2	120	5	4	5	4
3	53	5	4	4.9	4
4	67	4.1	3.81	3.83	3
5	53	3.6	3.3	4.18	3.45
6	40	3.27	3	3.09	3
7	75	3.72	3.81	3.45	3.63
8	40	3.81	3.36	3.63	3.45
9	38	4.8	4	4.8	4
10	45	4.1	4	4.2	4
11	51	4	3.6	4.4	4
12	87	nd	nd	3.8	3.2
13	57	4.2	4.2	3.9	3.45
14	54	3.81	3.36	3.81	3.41
15	57	3.9	3.45	4.18	3.9
16	38	4.6	3.8	4	3.8
17	61	4	4	4.6	4
18	41	4.6	4	4.6	4
19	100	3.81	3.09	3.81	3.63
20	61	4.5	4	4.4	4
21	60	4.8	4	5	4
22	63	4.45	3.81	4.27	3.54
23	84	3.81	3.63	4.5	4
24	88	4.2	3.8	4.4	3.8
25	89	4.2	4	4.2	4
26	135	4.09	3.36	4.2	3.6
27	129	3.8	3.2	4.2	3.2
28	58	4	3.45	4.4	3.8
29	28	3.63	3.63	3.5	3.16
30	57	4.3	4	4.3	4

low, the vascular leakage rate of group 3 patients was statistically significantly higher ($p < 0.05$). The nasal retinal vascularization was 3.68 ± 0.33 units (3.0–4.0) in group 1, 3.78 ± 0.29 units (3.0–4.0) in group 2, and 3.49 ± 0.32 units (3.0–4.0) in group 3. The temporal retinal vascularization was 4.1 ± 0.46 units (3.09–5.0) in group 1, 4.2 ± 0.41 units (3.80–5.0) in group 2, and 4.2 ± 0.44 units (3.09–5.00) in group 3, as well. Vascular development between groups was not statistically significant ($p > 0.05$).

Discussion

Anti-VEGF agents have recently utilized extensively for the treatment of ROP in many centers. Rapid regression of the disease after the injection and the ongoing progress of retinal vascularization lead to the anti-VEGF agents being preferred as first choice of treatment in zone I cases rather than the laser treatment [12, 19]. Laser-induced posterior synechia, cataract, phthisis bulbi, angle-closure glaucoma, retinal detachment, visual field loss, strabismus, and high myopia

rates decrease with the prioritized use of IVB, especially in zone I cases [20–24].

Although the IVB application has gained popularity in recent years, its possible local and systemic side effects have not been fully elucidated, and there is no consensus on how and how often the follow-ups are to be performed. Recurrences were seen at early and late term in some cases after the treatment, and these recurrences verified that the effect of anti-VEGF agents is temporary as it also turned out in our study [14, 25–27]. Mintz-Hittner et al. [7] reported in their study that infants with low birth weight, low gestational week, and that were hospitalized for long term; and patients with disease in zone I and diagnosed with APROP were in a higher-risk group in terms of recurrence.

Infants treated with IVB on diagnosis of APROP developed tractional retinal detachment after recurrence at the age of 2.5 years in a study [25]. The recurrences are a threatening condition; some of the eyes had progressed to stage 5 ROP in another study in which recurrence was found in 17 eyes of nine patients [26]. It was also reported that recurrence rate was higher in APROP in comparison with classic ROPs both of which had been treated with IVB and followed by FFA [28]. Although regression was observed in all eyes with single-dose bevacizumab application in patients with APROP in our study, recurrence was observed in 18 (30.5%) eyes during follow-ups. We performed second dose injections in 6 (10.1%) of the eyes with recurrence, and left others for spontaneously regression. Second dose of IVB was applied to infants with recurrence, who were at low gestational week and had low birth weight. Although eyes with single dose and two doses of IVB did not form a balanced group, no statistically significant difference was found between the groups in terms of birth weight and gestational week in our study. However, infants who had second dose of IVB have low birth weight and low gestational week, which might indicate that more attention should be paid to the follow-up of patients with these features. As infants treated with IVB were followed with frequent intervals in our clinic, recurrence and/or retinal detachment was averted by early intervention, and finally anatomical and functional success was achieved after the second treatment. This result proves that the effect of anti-VEGF agents in the treatment of ROP can be temporary which would not cover whole disease process. In the light of this information, the necessity of close follow-up was established in order to prevent blindness that might result from recurrences at early or late term until development of complete retinal vascularization or ablation of avascular area with laser, especially for those with risk factors for recurrence [14, 25–27].

With the introduction of FFA in ROP follow-up, recurrences that could not be detected through ophthalmoscopic scan, vascular abnormalities, and the state of retinal vascular development can be easily demonstrated in cases that received anti-VEGF treatment. With FFA, the presence of retinal pathologies were demonstrated such as halted retinal vascularization, occurrence of vascular leakage, loss of normal dichotomous branching, arteriovenous anastomoses, circumferential vessel formation, capillary malformations, focal dilatations, abnormal choroidal filling patterns, hyperfluorescent lesions in the macula, absence of foveal avascular zone, and hypoperfusion [15, 18, 29]. All these findings suggest that FFA is more valuable than ophthalmoscopic examination and that the anti-VEGF agents that are applied actually cause more abnormalities than the findings seen in the examination.

The presence of vascular leakage is the most important finding indicating severe ROP and surgical requirement, and today it can be easily detected by pediatric imaging techniques [29]. Tahija et al. [14] performed FFA in 20 eyes of 10 infants they treated with IVB and found vascular leakage in 9 of the eyes. Gonzales et al. [28] demonstrated a higher rate of leakage with FFA in APROP cases treated with IVB compared to classical ROP cases. Lepore et al. found vascular leakage by FFA in 65% of IVB treated eyes of patients at 4 years of age. They have concluded that the leakage after treatment indicated persistence of the disease [30].

In many studies it was demonstrated that retinal vascular development was not completed in some of the premature infants treated with anti-VEGF [14, 18, 28–30, 32]. When Tahija et al. [14] evaluated infants that were given a single dose of IVB with FFA, they observed that vascularization was not completed in 11 of 20 eyes. Lorenz et al. [18] evaluated the infants with their own self-developed method and found that approximately 12.5% of the eyes did not achieve acceptable retinal vascularization. In one study, it was observed that in only 9% of infants with IVB, retinal vascularization was complete at 54th

PMW. It was stated that the vascularization of infants could possibly be completed during the long follow-up period, but that the follow-ups and examinations would be difficult to keep up as the infant grew, and that the patients should be examined very frequently and this necessity would increase the patient load [32]. According to our FFA results, it was observed that 8% of the eyes achieved complete retinal vascularization (temporal rate $\geq$ 5 units), but in a significant portion (34%) the development of vessels were below the acceptable limit ($<$ 4 units in the temporal region). For the eyes with retarded vascularization, laser photocoagulation was applied to those in which leakage was detected, and those free of leakage were listed for follow-up to be re-evaluated with a second FFA after 6 months. With these results, it was demonstrated that continuation of retinal vascular development was an important advantage after rapid regression was achieved with IVB in patients diagnosed with APROP, but that vascularization was not completed in a significant part of the cases. In addition, it was mutually agreed through the conducted studies that laser photocoagulation had an important place in protecting the eyes from possible serious complications that might arise from avascular area during follow-ups.

When the group of patients who received the second dose of IVB was considered, it was observed that none of the 6 eyes reached the point of complete retinal vascularization in the nasal or temporal areas. Evaluation of acceptable vascularity revealed that only one eye (16.7%) reached this boundary that was considered as safe in the temporal. Although the number of eyes receiving single and two doses of IVB fell short of forming a balanced group and thus was rendered insufficient to provide a correct statistical result, when the two groups were compared, it was observed the vascular development of the recipients of two-dose IVB was retarded statistically ($p < 0.004$). Although there are no studies comparing this condition in the literature, it is thought that anti-VEGF treatment is successful in remitting the disease, but it further decelerates vessel development especially through repeated injections. Since the distribution of eyes with single and two doses of IVB is not stable in our study, it is thought that this result should be confirmed with a larger number of cases. Since the eyes with single and two doses of IVB were not normally distributed in our study, it is thought that this result should be confirmed with a larger number of cases.

Our study, which evaluated the recurrence, vascular leakage, and vascular development of the patients who underwent IVB with the diagnosis of APROP, showed that infants born with low birth weight and low gestational week should be closely followed up even after the disease remission occurs. The infant grows over time during the follow-ups, and proper examination with binocular indirect ophthalmoscopy becomes impossible, which raises the need for frequent examinations under anesthesia. Frequently repeated examinations which become progressively more difficult may cause the family to fail to bring the patient over for follow-ups, which may eventually cause the infant to face the risk of blindness due to the possibility of future recurrences. In our country, in the light of studies in which FFA applications have been introduced to the usage of pediatric cases as well, application of this diagnostic method with periodical intervals is observed to yield highly valuable results especially for the follow-up of ROP cases that were treated with anti-VEGF. The cases in which occurrence of leakage going undetected with ophthalmoscopic examination as well as halted vascular development are detected by means of FFA can be treated in the early period with laser photocoagulation. This feasibility reduces the patient load of patients to be examined at the clinic and makes it possible to perform the follow-ups relatively more safely. In the future, by studies performed with FFA would provide a common consensus on the follow-up of infants who were treated with IVB, and would ensure that both the physicians engaged in this work and the infants treated were safeguarded.

In totally, presence of leakage was observed in 15.3% of the eyes with FFA in our study, highest in the latest FFA group. Although leakage was considered as a risk factor for the development of severe ROP in a study, vascular leakage along with the disease in a patient with type 2 ROP was regressed without an intervention during the follow-up [31]. On the other hand, other cases with leakage were found to develop type 1 ROP and were treated with IVB in the same study. After IVB treatment, regression of the leakage without applying an additional laser photocoagulation could be demonstrated by monitoring with periodical FFA. However, we performed laser photocoagulation in all of these eyes because of not coming to follow-up

examinations and potential risk of blindness related to retinal detachment according to Gonzales's and Lorenz's studies [28, 29].

Limitation

We regret the possible occurrence of spontaneous regression which might decrease the ratio of leakage especially in the third group. In contrary, we found highest ratio in that group and we do not know the extent of spontaneous regression in the time which elapsed until we have performed FFA. We applied laser photocoagulation at the beginning to the eyes with leakage after IVB to prevent retinal detachment and blindness. The importance of long follow-up FFA to give enough time for spontaneous regression was not evaluated in our patients who had routinely laser in case of leakage.

In conclusion, the difference in the ratio of leakage in our three groups of the babies, who have similar ages or other demographical characteristics, may suggest that it is coincidental or leakage persisted in the eyes for a long time (as indicated in previous studies). Paradoxically, the leakage was unexpectedly found to be higher in this last FFA group. It might mean that leakage which is seen with FFA but not indirect ophthalmoscopy could result in a second peak beyond a usual early first peak or all recurrences occur in a wide range than we expect. Although no pathology was detected in the ophthalmoscopic examination of the eyes, we believe that detection of leakage by the angiography enabled a chance of early intervention to the patients and probably prevented some potential blindness that would develop in the future. Therefore, there are two approaches depending on FFA follow-up after the treatment of APROP. First one is early follow-up and to treat with laser (or another treatment) whenever a leakage was demonstrated. Second one is a long and close follow-up (up to 4 years or longer) and to reserve laser to a worsening leakage. Further randomized trials are needed to make a definitive conclusion in comparison with two approaches.

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